MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA
***NICOLAE TESTEMIŢANU* STATE UNIVERSITY**
OF MEDICINE AND PHARMACY

ROBU Maria, BURUIANĂ Sanda,
TOMACINSCHII Victor, GOLUB Aliona

CLINICAL FEATURES, DIAGNOSIS AND TREATMENT OF IRON DEFICIENCY ANEMIA

(methodological guide for students)

CHIŞINĂU
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DESCRIEREA CIP A CAMEREI NAŢIONALE A CĂRŢII DIN REPUBLICA MOLDOVA

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CONTENTS

LIST OF ABBREVIATIONS

IDA – iron deficiency anemia
MCV – mean corpuscular volume
MCH – mean corpuscular hemoglobin
MCHC – mean corpuscular hemoglobin concentration
Hb – hemoglobin
TIBC – total iron binding capacity
LIBC – latent iron binding capacity
TS – transferrin saturation
PNH – paroxysmal nocturnal hemoglobinuria
CRP – C-reactive protein
PHCI – Public Healthcare Institution
ESR – erythrocyte sedimentation rate
CD – cluster of differentiation

IRON-DEFICIENCY ANEMIA

DEFINITION

Iron-deficiency anemia (IDA) is a type of anemia characterized by a deficiency in hemoglobin synthesis due to a decrease in the total body iron content. It is the most common form of anemia and one of the most prevalent human pathologies [6, 7, 9, 14, 24]. Iron-deficiency anemia accounts for approximately 80-85% of all anemia cases [8, 9, 11]. Iron-deficiency anemia affects individuals across all age groups, but is most common in children and women of reproductive age [1, 2, 5, 21, 24, 25, 26]. It occurs in 8-15% of women of reproductive age, while iron deficiency is present in approximately one in three women [8, 20, 23]. According to the World Health Organization, iron deficiency affects 24.8-30% of the global population, or around 1.3 billion people [7, 23]. Iron deficiency affects approximately one-third of the population [15, 20, 26]. Even in countries where dietary iron intake is adequate, foods are fortified with iron, and iron supplements are widely used, iron-deficiency anemia remains a problem. For example, more than 20% of young girls and women of reproductive age have depleted iron stores [8, 21]. Approximately 50-60% of pregnant women suffer from iron-deficiency anemia, and iron deficiency is found in 70% of pregnant women. Latent iron deficiency is present in nearly all women in late pregnancy [7, 8, 13]. Iron-deficiency anemia is common worldwide, with a significantly higher prevalence in socially and economically underdeveloped countries [21, 22]. Consequently, iron-deficiency anemia affects a large proportion of the global population *(Fig. 1).*

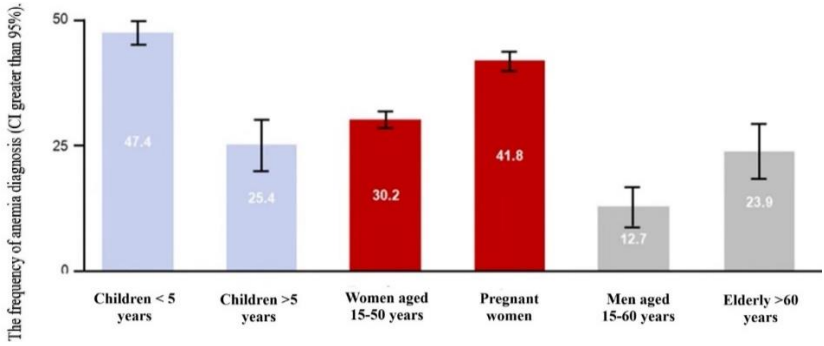

Figure 1. Frequency of iron-deficiency anemia in different population groups

PREFACE

This methodological guide covers the essential topics necessary for students to recognize and diagnose iron-deficiency anemia, as well as to develop treatment strategies. It provides a clear and accessible presentation of the subject matter related to IDA, aimed at helping students master the diagnosis and management of this condition. The primary objective is to support medical students in their learning. The defined concepts aim to enrich knowledge in the field and are useful during the stages of knowledge assessment. Special attention is given to the clinical work of students both in in-patient and out-patient settings, including practical activities, tests and case studies. To facilitate understanding of the material, this methodical guide is supplemented with graphical presentations (tables, figures, diagrams), images, clinical cases, and tests.

The seminar duration is 4 hours.

Aim of the seminar. To study the epidemiology, etiology, pathogenesis, and clinical manifestations of iron-deficiency anemia (IDA), as well as the laboratory and instrumental methods used to diagnose it. The seminar will also focus on identifying the causes of IDA and understanding the principles of its treatment.

Seminar objectives

1. To acquire knowledge about the etiology, epidemiology and pathogenesis of IDA;
2. To develop an understanding of the clinical and hematological features of IDA;
3. To gain practical skills in diagnosing IDA;
4. To learn the differential diagnosis of IDA;
5. To understand the general principles of treating patients with IDA.

Seminar venue

1. Hematology Department, *Nicolae Testemitanu* SUMPh
2. Hematology Units within the Hematology Department, PHCI Oncological Institute, Republic of Moldova
3. Hematology practice settings within the Diagnostic Consultative Center, PHCI Oncological Institute, Republic of Moldova

Methods and materials used in the seminar

Teaching methods used. To effectively acquire knowledge and achieve the objectives, various teaching methods and procedures are used, including:

- Lecturers: narration, description, explanation, and demonstration
- Discussions: group discussions, problem-solving activities.
- Synthesis

In practical work, forms of independent, frontal, group and interactive activity are used.

Assessment methods

- oral questioning
- clinical case studies
- problem solving
- tests
- summative assessments
- individual work
- assessment of practical skills
- exam

Materials for the seminar. Teaching materials such as tables, diagrams, algorithms, images, and international guidelines are used to deepen the understanding of IDA. PowerPoint presentations are also used during the seminars.

QUESTIONS FOR SELF-STUDY

1. Epidemiology of iron-deficiency anemia
2. Etiology of iron-deficiency anemia
3. Pathogenesis of iron-deficiency anemia
4. Clinical picture of iron-deficiency anemia
5. Stages of iron-deficiency anemia
6. Laboratory tests in iron-deficiency anemia
7. Methods of investigating the cause of iron-deficiency anemia
8. Diagnosis of iron-deficiency anemia
9. Differential diagnosis of iron-deficiency anemia
10. Principles of treatment of iron-deficiency anemia

EPIDEMIOLOGY OF IDA

According to the World Health Organization, iron deficiency affects about 30% of the global population, approximately 1.3 billion people [7, 23]. It is present in about one-third of the population [20, 26]. Even in countries where dietary iron intake is generally sufficient, food products are fortified with iron, and iron supplements are widely used, iron-deficiency anemia remains a significant issue. For example, more than 20% of young girls and women of reproductive age have depleted iron stores [8,21]. Approximately 50-60% of pregnant women suffer from iron-deficiency anemia, and iron deficiency is found in 70% of pregnant women. By the end of pregnancy, nearly all women exhibit latent iron deficiency [7, 8, 13].

ETIOLOGY OF IDA

To better understand the causes of IDA, it is important to have knowledge about iron metabolism in the body. The total iron stores in the body amount to approximately 4-5 grams. About 75% of this iron is found in the hemoglobin of erythrocytes, while 15-16% is stored in ferritin and hemosiderin, which serve as iron stores in tissues. An additional 3-4% is present in myoglobin, and the remaining iron is involved in respiratory enzymes. Iron plays an essential role in the functioning of various cellular mechanisms, participating in oxidative processes and the metabolism of all cells [10, 13, 14, 17]. It is known that the body can absorb up to 2-2.5 mg of iron daily. Physiological losses of iron, which occur through skin desquamation, sweat, saliva, shedding of the gastrointestinal epithelium, urine, and other processes, amount to 1-1.5 mg per day. Therefore, there is a balance between absorption and loss. However, only 0.5-1.0 mg of absorbed iron remains available for hematopoiesis, while the daily requirement for this process is 20-25 mg. This additional iron is obtained from the physiological breakdown of erythrocytes, which releases iron that is then reused by the body. The question arises: Why is only 2 mg of iron absorbed, even when a proper diet provides 16-18 mg of iron daily? It should be noted that dietary iron is primarily in the trivalent state, but it is absorbed only in the bivalent state. Approximately 6-7 mg of dietary iron is converted into the bivalent form in the stomach, but not all of it comes into contact with the receptors of the epithelial cells in the small intestine. As a result, only up to 2 mg of iron is absorbed from food [8, 13].

Iron absorption occurs in the proximal region of the small intestine, predominantly in the duodenum, where receptors for bivalent iron are located [8,16]. When iron enters the stomach with food, it is in the trivalent form. In the stomach, proteolytic enzymes release iron from the food, and ascorbic acid converts it to the bivalent form. Iron reaches the duodenum and the proximal portion of the small intestine, where binding receptors for bivalent iron are located. The endothelial cells in this region contain a protein similar to transferrin, which binds to iron ions and transports them to the basement membrane. From there, the iron is taken up by transferrin and transported to the bone marrow, as well as other

organs and tissues. In the blood, iron is bound to transferrin, a transporter protein synthesized in the liver. Transferrin, under both physiological conditions and during iron deficiency, facilitates the transfer of iron to erythrocyte precursors in the bone marrow.

Normally, only one-third of transferrin is saturated with iron, and the iron-bound transferrin is referred to as serum iron. Iron absorption in the intestine is well-regulated. When transferrin is saturated, it does not accept iron ions from the intestinal epithelial cells. This iron binds to apoferritin, forming ferritin granules, and is eliminated from the body along with the physiological desquamation of the intestinal epithelium. Thus, during oral administration of iron preparations at therapeutic doses, it is not possible to overload the body with iron. At the bone marrow level, the membranes of erythrokaryocytes contain binding receptors for iron-saturated transferrin. Once transferrin enters the erythrokaryocytes, the iron is released, with approximately 90% reaching the mitochondria and 10% remaining in the cytoplasm. The iron in the cytoplasm binds to apoferritin, forming ferritin granules that serve as iron stores within the erythrokaryocytes. Erythrokaryocytes containing ferritin granules are referred to as sideroblasts. In the mitochondria of erythrokaryocytes, iron binds to protoporphyrin IX in the presence of the enzyme heme synthetase to form heme, which then binds to globin to produce hemoglobin. The iron-free transferrin is returned to the bloodstream to transport new iron. Thus, iron plays a crucial role in the multi-step process of hemoglobinization of erythrocytes *(fig. 2).* Heme cannot be synthesized in erythrocytes, as they lack binding receptors for iron-saturated transferrin on their surface.

Some of the iron bound to transferrin is used for erythropoiesis, while the rest is stored in the body as ferritin and hemosiderin. Iron stores in the form of ferritin are present in all tissue cells throughout the body. Plasma ferritin levels correlate closely with the body's total iron stores. Therefore, plasma ferritin levels indicate the iron stores in tissues, which are an important clue in confirming the diagnosis of iron-deficiency anemia [1, 10, 13]. Iron from ferritin is released more readily than iron from hemosiderin, where the release process is slower. Understanding

iron metabolism helps identify the causes of iron-deficiency anemia, because iron metabolism can be dysregulated at any stage, from iron absorption and to hemoglobin synthesis.

The following factors may contribute to the development of iron-deficiency anemia:

- insufficient iron intake from the diet
- increased iron requirements of the body
- increased iron loss
- dysregulation of iron absorption

Sometimes, iron deficiency may result from a combination of two or more mechanisms, rather than a single cause.

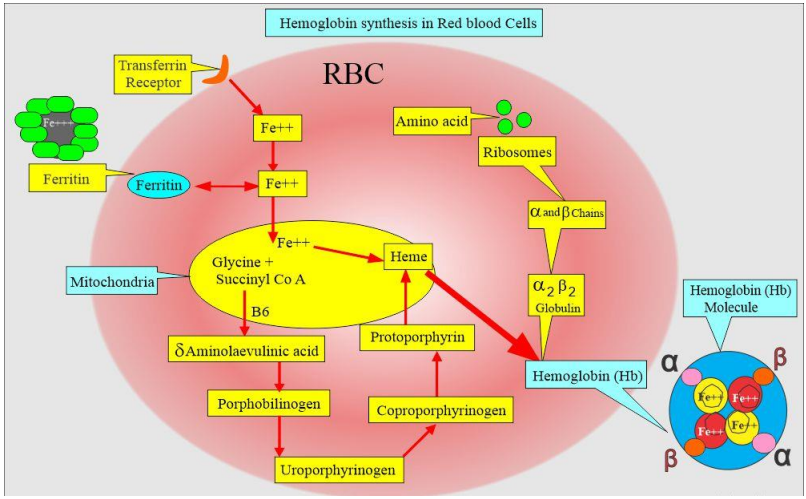

Figure 2. Mechanisms of hemoglobin synthesis

Iron deficiency in adults can occur in individuals who consume primarily dairy or have vegetarian diets. Although iron is found in various foods, it is better absorbed from meat, as it is more easily released and taken up by the body. While legumes are rich in iron, the iron they contain is harder to release and absorb. Additionally, dairy products can inhibit iron absorption.

Dietary deficiency is the predominant cause of iron deficiency in children aged 6 to 18 months. Newborn infants have iron stores of 300-500 mg, which

are depleted within 4-6 months, while premature infants have iron stores of about 200 mg, depleted within 1-2 months. Predominantly milk-based feeding and delayed introduction of complementary foods can lead to the development of iron deficiency in infants. In children up to 1-1.5 years of age, iron-deficiency anemia is primarily of dietary origin [3, 8].

Increased iron requirements are common in pregnant and lactating women. Iron-deficiency anemia occurs in 50-60% of pregnant women *(Fig. 3)*, while iron deficiency affects up to 70% of cases [8, 13].

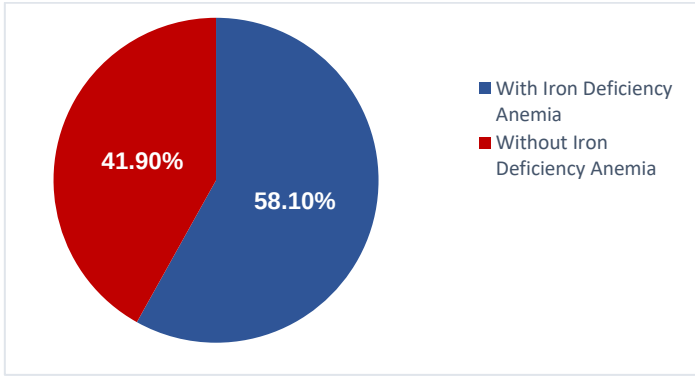

Figure 3. Frequency of iron-deficiency anemia in pregnant women

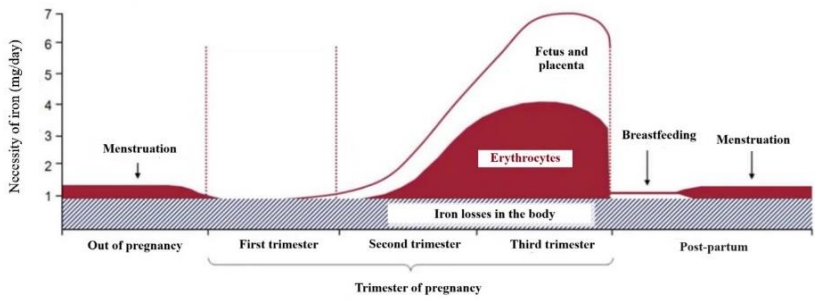

Figure 4. Estimated daily iron requirements for a pregnant woman weighing 55 kg (Bothwell et al., 2000)

Iron requirements are also higher in children under 1 year of age due to the rapid increase in body mass and blood volume. During the first year of life,

a child gains 800-1000 g of weight per month, contributing to the increased iron requirements. Premature babies have a more rapid increase in body mass during the postnatal period, leading to the quick depletion of their limited iron reserves (100-200 mg). As a result, iron-deficiency anemia can develop as early as the second month of life. In some adolescents, the rapid growth in body mass over a short period also creates conditions for increased iron requirements, potentially leading to the development of iron-deficiency anemia.

The most common cause of iron-deficiency anemia is chronic bleeding [1, 2, 8, 18]. A loss of 2 mL of blood equates to approximately 1 mg of iron. Chronic bleeding leads to iron-deficiency anemia in about 75-80% of cases. Since 75% of the body's iron is contained in hemoglobin, blood loss results in iron depletion, as iron is lost along with the blood during hemorrhage. Iron-deficiency anemia develops when iron losses exceed the amount of iron absorbed daily from food. One of the most common causes is menometrorrhagia in women of reproductive age. Metrorrhagia may result from conditions such as uterine fibroids (fibromyoma), polyps, or uterine cancer. The second most common cause is chronic bleeding from the gastrointestinal tract, which is more prevalent in men and menopausal women [1, 8, 13, 18]. These hemorrhages are diverse and can be caused by conditions such as esophageal varices, esophageal cancer, hiatal hernia, erosive gastritis, gastric ulcer, gastric cancer, duodenal ulcer, polyps, diverticular disease (diverticula), Meckel's diverticulum, Crohn's disease, intestinal parasitic infections (trichocephalus, tapeworm, duodenal hookworm), ulcerative colitis, colon cancer, hemorrhoids, and anal fissures. Bleeding can also result from hemostatic dysregulation. Additionally, iron-deficiency anemia may develop in regular volunteer blood donors who donate blood every 2-3 months.

Another mechanism for the development of iron-deficiency anemia is the dysregulation of iron absorption, which can occur in cases such as Billroth II stomach resection, gastrectomy, extensive resection of the proximal region of the jejunum, chronic enteritis, malabsorption syndrome, or iron-transporting protein deficiency (hypotransferrinemia), also known as protein-deficiency anemia [8, 18].

These are the causes that can lead to the development of iron-deficiency anemia. However, in some cases, multiple factors may contribute to its

development rather than a single cause. For example, in adolescent girls, there may be two or even three contributing mechanisms such as increased iron requirements, menstrual losses and insufficient dietary iron intake. These factors should be considered when developing an investigation plan for each individual patient.

PATHOGENESIS IDA

Is a pathological process that arises from a lack of iron in the body. Iron is essential for the synthesis of hemoglobin, and when iron is deficient, hemoglobin synthesis is impaired, leading to anemia, which clinically presents as an anemic syndrome. Additionally, iron is a component of enzymes such as cytochrome C oxidase and catalase, playing a crucial role in cellular oxidative processes. Iron deficiency disrupts the metabolism of all cells, particularly those with high mitotic activity, such as the endothelial cells of the gastrointestinal tract. This disruption leads to dystrophic processes and eventually atrophy of the mucosa throughout the digestive tract. Symptoms resulting from the cellular metabolic dysregulation caused by iron deficiency in tissues are collectively referred to as sideropenia or sideropenic syndrome.

CLINICAL FEATURES OF IRON-DEFICIENCY ANEMIA

The clinical features of IDA includes two clinical syndromes: anemic and sideropenic. The anemic syndrome is characterized by general weakness, fatigue, dizziness, tinnitus, shortness of breath during physical exertion, palpitations, skin pallor, tachycardia, and sometimes a systolic murmur at the apex of the heart. The severity of these symptoms depends on the extent of hemoglobin reduction.

IDA classification according to the degree of anemia:

- Grade I – hemoglobin content 9.1-11.0 g/dL
- Grade II – hemoglobin content 7.1-9.0 g/dL
- Grade III – hemoglobin content < 7.1 g/dL

The sideropenic syndrome is specific to iron-deficiency anemia and is absent in other types of anemia because it results from iron deficiency in the tissues. Clinically, it is manifested by dry skin, frequent heel fissures, and angular stomatitis (fissures at the corners of the mouth, also known as angular cheilitis) *(fig.5).*

The hair is dry and brittle, breaking easily and shedding profusely *(Fig. 6).*

Figure 5. Angular cheilitis

Figure 6. Dry and damaged hair. Hair loss.

The nails become thin and brittle, break easily, and may split. Longitudinal striations may also appear *(fig.7).*

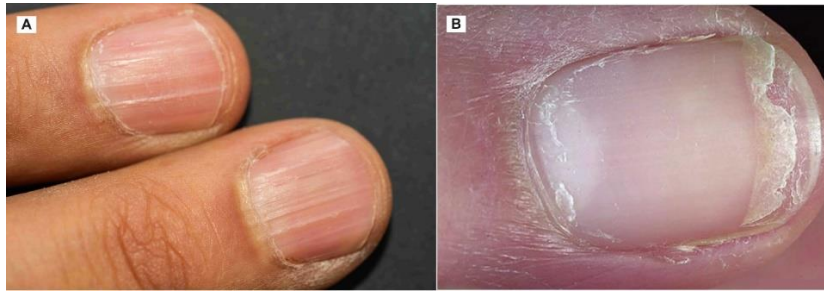

Figure 7. Nail appendage changes in iron-deficiency anemia: **A.** Longitudinal nail striation; **B.** Increased nail fragility associated with nail splitting.

In iron-deficiency anemia, a nail alteration known as "koilonychia" may also occur. Koilonychia refers to abnormally thin nails, usually of the hands, that have lost their normal convexity and become flat or even concave (spoon-shaped) *(Fig. 8).*

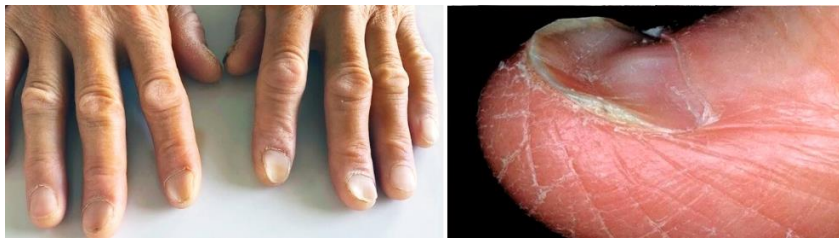

Figure 8. Nail changes in iron-deficiency anemia: koilonychias

Dryness occurs in the oral cavity due to decreased function of the salivary glands, caused by the atrophy process, which leads to reduced saliva production. Sideropenic dysphagia frequently develops, making swallowing painful and difficult. The food bolus is particularly difficult to swallow, especially hard foods such as bread, meat, and eggs, leading to a sensation of a "lump in the throat". This occurs because the food bolus is

not well processed in the oral cavity due to the reduced flow of saliva, and atrophy of the esophageal mucosa makes it harder for the food bolus to slide down the esophagus. The symptom of sideropenic dysphagia is associated with Plummer-Vinson syndrome, which develops gradually due to atrophy of the hypopharyngeal mucosa at the junction between the pharynx and esophagus. The lesion can narrow the lumen of the pharyngoesophagus into a cuff, which, in cases of pronounced iron deficiency, can cause a true stricture. Patients often feel the food bolus as it travels down the esophagus and may develop esophageal spasms. Additionally, patients may experience stomach rumble or abdominal sound (bubble gut or borborygmus) due to digestive disorders.

In patients with IDA, dystrophic and later atrophic disorders may occur throughout the gastrointestinal tract with the development of conditions such as gastritis, enteritis, and colitis. Sideropenic syndrome is characterized by abnormal tastes and smells, commonly referred to as "pica chlorotica". Patients may crave substances like chalk, soil, raw pasta, rice, raw meat, salt, coffee beans, lemon, and raw fish. They also often enjoy the smells of acetone, paint, petrol, and mold. This phenomenon is thought to be related to iron deficiency in the brain, which affects the gustatory and olfactory areas. As a result, abnormal taste and smell develop, which disappear after treatment, confirming that they are caused by iron deficiency. It is important to note that patients may only exhibit signs of anemia syndrome. The signs of sideropenic syndrome can often be identified through additional targeted questioning of the patient and a thorough objective examination.

Stage I, or prelatent, is characterized by a decrease in ferritin only, while serum iron content and hemoglobin levels remain within the normal range. In stage II, or latent, there is a decrease in ferritin as well as in serum iron, although hemoglobin levels remain within normal limits. In stage III, or iron deficiency anemia, ferritin is significantly reduced, serum iron is also decreased, and hemoglobin levels are lower than normal. First, ferritin decreases, followed by serum iron, and finally hemogloin levels. These developmental stages have practical diagnostic

and treatment significance. Since ferritin decreases first, followed by serum iron, and lastly hemoglobin levels, these data are critical for diagnosis. Patients with IDA should be diagnosed not in stage III, but at an earlier stage, preferably in the prelatent or at least latent stage. Therefore, measuring serum ferritin and serum iron should be routine methods for the early diagnosis of patients with IDA.

STAGES OF IRON DEFICIENCY

Iron deficiency develops slowly. There are three stages of iron deficiency [8, 9, 16] *(Table 1).*

Table 1

Stages of iron deficiency

Iron deficiency stage	Serum ferritin level	Serum iron	Hemoglobin level
Prelatent iron deficiency	Low	Normal	Normal
Latent iron deficiency	Considerably low	Low	Normal
Iron deficiency anemia	Very low	Low	Low (anemia)

When treating patients with IDA, hemoglobin levels normalize first, followed by the restoration of iron reserves in tissues over 4-6 months, which is confirmed by ferritin levels returning to the normal range. Therefore, treatment is long-term and should continue not only until hemoglobin levels normalize but also until ferritin levels are restored.

LABORATORY TESTS USED TO DIAGNOSE IRON-DEFICIENCY ANEMIA

The diagnosis of iron-deficiency anemia is confirmed through laboratory methods. First, a complete blood count is performed to assess the decrease in hemoglobin level and erythrocyte count. There is no correlation between the decrease in hemoglobin and the erythrocyte count.

The hemoglobin level is much lower than the erythrocyte count, resulting in a decreased color index. The reticulocyte count is normal. The number of leukocytes and platelets is usually within the normal range, but in 30% of cases, hyperthrombocytosis can occur. The leukocyte count is unchanged.

Erythrocyte morphology, characterized by hypochromia and anisocytosis (microcytosis), is important in establishing the diagnosis *(Fig. 9)* [4, 5, 13]. The mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) are decreased. Sometimes, the hypochromia is very pronounced, and the erythrocytes appear as rings, referred to as annulocytes. In cases of severe iron deficiency, poikilocytosis (variations in shape) may also occur due to the deformation of the erythrocyte membrane.

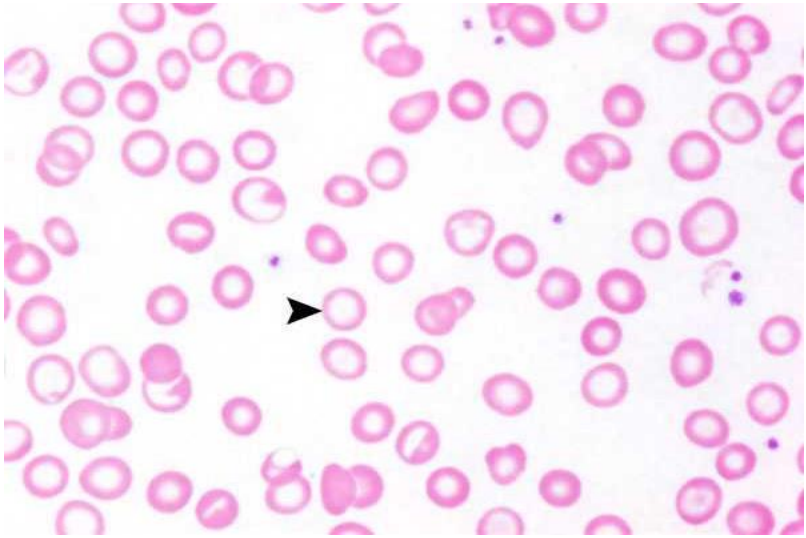

Figure 9. Peripheral blood smear (hypochromia, microcytosis)

A medulogram from bone marrow aspiration is usually not necessary, but if performed, it may show moderate hyperplasia of the erythroid series, with small, irregularly shaped erythrokaryocytes and ragged cytoplasmic membrane. Shrinkage of sideroblasts may also be observed.

Serum iron levels are decreased. It is important to correctly collect blood for serum iron testing. The patient should not receive any iron supplements for at least five days prior to the test, as taking iron supplements can result in normal or elevated serum iron levels at the time of blood collection.

The total iron-binding capacity (TIBC) and latent iron binding capacity (LIBC) increase, while the transferrin saturation coefficient (SC) decreases [9, 16]. To assess the body's iron reserves, serum ferritin levels should be measured, which are decreased in iron deficiency anemia [1, 9].

METHODS FOR INVESTIGATING THE CAUSE OF IRON-DEFICIENCY ANEMIA

Fecal occult blood test
Fecal examination for helminths
Fibrogastroduodenoscopy
Fibrocolonoscopy
Rectosigmoidoscopy
Stomach radiography with small bowel follow-through
Barium enema (irrigoscopy)
Gynecological examination (for women)

DIAGNOSIS OF IRON-DEFICIENCY ANEMIA

The diagnosis of iron-deficiency anemia is established based on the presence of anemic and sideropenic syndromes in the clinical picture and a complete peripheral blood analysis. This analysis reveals decreases in hemoglobin levels, the number of hypochromic and microcytic erythrocytes, MCV, MCH, MCHC, ST, serum iron, and serum ferritin, as well as increases in TIBC and LIBC.

Diagnostic algorithm in iron-deficiency anemia

I. IDA suspection

Anemic syndrome (general weakness, dizziness, dyspnea during physical exertion, tinnitus, headache, palpitations, pale skin, tachycardia, etc.)

Sideropenic syndrome (dry skin, cracked heels, brittle nails, nail splitting and layering, easy hair breakage, hair loss, dry mouth, angular stomatitis, altered sense of taste and smell, etc.)

⇩

II. IDA confirmation

1. Complete Blood Count (CBC) with platelets and reticulocytes (anemia, hypochromia, microcytosis)
2. Serum iron (decreased)
3. Serum ferritin (decreased)

⇩

III. Determining the cause of IDA

1. Anamnesis (insufficient iron intake, increased iron requirements, increased iron loss, impaired iron absorption)
2. Fecal occult blood test
3. Fecal examination for helminths
4. Rectosigmoidoscopy
5. Fibrogastroduodenoscopy
6. Colonoscopy
7. Stomach radiography with small bowel follow-through
8. Irrigoscopy
9. Gynecological examination (for women)

DIFFERENTIAL DIAGNOSIS OF IRON DEFICIENCY ANEMIA

The differential diagnosis of iron-deficiency anemia should be performed with other anemias characterized by hypochromia of erythrocytes, such as paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli disease), thalassemia, sideroblastic anemia, anemia of chronic diseases.

In patients with paroxysmal nocturnal hemoglobinuria (PNH), an acquired hemolytic anemia, iron deficiency may develop due to hemoglobinuria. Erythrocytes are hypochromic, and serum iron levels are typically low, although serum iron may temporarily increase during hemolytic crises. However, PNH differs from iron-deficiency anemia in that a

complete blood count reveals anemia accompanied by reticulocytosis, indicating hemolysis, along with signs of intravascular hemolysis such as hemoglobinemia, hemoglobinuria, and hemosiderinuria. Diagnostic tests for PNH, such as the Ham test and sucrose test, are positive. The diagnosis of PNH is confirmed by flow cytometry, which shows a lack of expression of the clusters of differentiation CD55 and CD59 on the surface of the erythrocyte clone.

In thalassemia, which is a hereditary hemolytic anemia, erythrocytes are hypochromic, and many of them exhibit a hemoglobinized dot in the center, giving them the appearance of "target cells." A complete blood count shows reticulocytosis. Unlike in iron-deficiency anemia, serum iron and serum ferritin levels are elevated. Patients with thalassemia often present with signs of intracellular hemolysis and splenomegaly. The diagnosis and identification of the specific type of thalassemia are confirmed by hemoglobin electrophoresis.

Sideroblastic anemias are a heterogeneous group of disorders characterized by the accumulation of ferritin in the mitochondria of erythroblasts. In bone marrow smears stained with Perls' stain, iron overloaded mitochondria appear as granules that form a ring around the nucleus, known as ring sideroblasts. The presence of these sideroblasts is a key diagnostic criterion for sideroblastic anemia. In this condition, iron is not utilized effectively and is instead deposited in tissues and organs, leading to secondary hemosiderosis. Erythrocytes in patients with sideroblastic anemia are hypochromic and may exhibit anisocytosis (microcytes or macrocytes), as well as basophilic stippling**.** Laboratory findings typically show elevated serum iron, serum ferritin, and transferrin saturation, with low total iron-binding capacity (TIBC).

Anemia of chronic disease is caused by the development of relative iron deficiency due to the redistribution of iron in the body. This occurs because of the overproduction of hepcidin by hepatocytes, which leads to the sequestration of iron in macrophages, making it unavailable for erythropoiesis. Anemia of chronic disease can develop in patients with chronic inflammatory conditions, such as tuberculosis, pneumonia, chronic obstructive pulmonary disease, osteomyelitis, lung abscess, bronchiectasis,

pleural empyema, peritonitis, septic endocarditis, sepsis, systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, and malignant tumors.

In these patients, there is no decrease in total body iron, as evidenced by increased serum ferritin levels. Erythrocytes may be normochromic or hypochromic and microcytic. Laboratory findings typically show low serum iron, normal or low TIBC, low transferrin saturation, and elevated C-reactive protein (CRP). A bone marrow aspirate stained with Perls' stain reveals hemosiderin present or elevated in macrophages, but absent in sideroblasts. The presence of hypochromic anemia with normal or elevated serum ferritin, in association with a chronic inflammatory condition, indicates that the anemia is due to iron redistribution, helping to differentiate it from iron-deficiency anemia.

TREATMENT PRINCIPLES OF IRON-DEFICIENCY ANEMIA

The aim of IDA treatment is to normalize hemoglobin levels, erythrocyte count, and restore iron stores in the body (normalization of serum ferritin) [7,12, 16,19]. A wide variety of oral and parenteral drugs are available for the treatment of iron-deficiency anemia *(Fig. 10).* Oral therapy is prioritized in the treatment of iron-deficiency anemia [2, 6, 18, 24].

Treatment of iron deficiency anemia is carried out with bivalent iron-containing drugs in tablet form for oral therapy, such as Sorbifer (ferrous sulphate 320 mg + ascorbic acid 60 mg), ferrous sulphate, Hemofer (iron chloride), Folifer (ferrous sulphate 288 mg + folic acid 1 mg), Fersinol (lyophilized ferrous sulphate), Ferrofolgama (Iron sulphate), Tardiferon (ferrous sulphate sesquihydrate), Ferrogradumet (dried ferrous sulphate), Ferroplex (ferrous sulphate + ascorbic acid) and others. Additionally, trivalent iron preparations, such as Ferrum-Lek and Maltofer (polymaltose iron hydroxide) may be used. In recent years, a new generation of oral iron preparations has emerged, such as sucrosomal iron (e.g., Sideral Forte, Ferosom Forte and others), which contain iron pyrophosphate encapsulated in a liposomal capsule. Iron pyrophosphate is protected by a double phospholipid membrane. This coating ensures high tolerance and rapid absorption of trivalent iron pyrophosphate

within the liposomes. Additionally, the liposomal membrane prevents contact between the iron and the gastric mucosa, thereby avoiding oxidative effects and minimizing adverse effects such as epigastric pain, dyspeptic disorders (nausea, vomiting), constipation, and diarrhea.

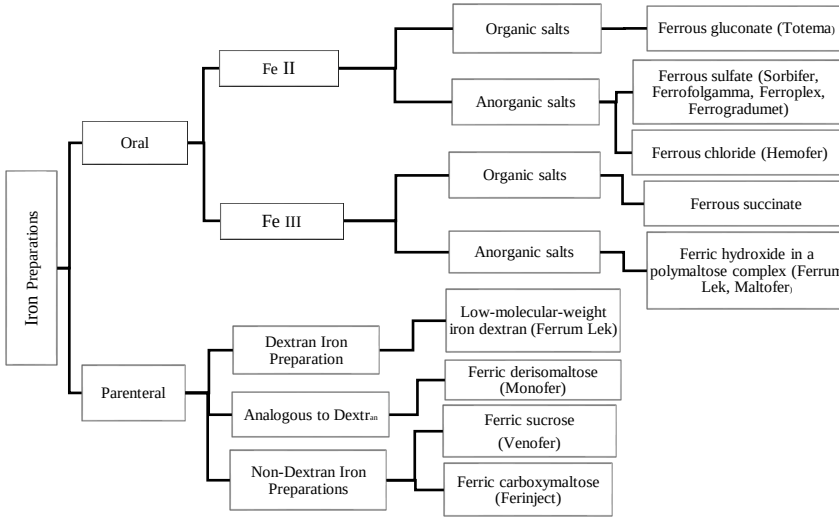

Figure 10. Conceptual classification of drugs used in the therapy of iron-deficiency anemia

One of the listed iron preparations should be taken as one tablet twice a day, 30-40 minutes before meals, with 100 ml of water or juice until hemoglobin levels normalize. It should not be taken with tea, coffee, milk, or dairy products. Tea, coffee, milk, and dairy products inhibit iron absorption [4, 13, 25]. After hemoglobin levels normalize, treatment should be continued at the same dose for 4-6 months (until ferritin levels are normalized). Concomitant administration of iron preparations with antacids, calcium supplements, oxalates, or phosphates should be avoided.

In cases where the cause of iron deficiency persists (e.g., hiatal hernia, ulcerative colitis, menorrhagia, hemorrhoids), it is recommended to take 2-3 tablets of an iron preparation per week as long as the underlying cause remains.

Iron preparations for parenteral use are administered according to absolute indications, such as digestive intolerance to oral iron preparations or impaired iron absorption [9, 18]. The intravenous iron therapy should include iron sucrose (Venofer), ferric carboxymaltose (Ferinject), and iron isomaltose (Monofer). All paranteral preparations should initially be administered very slowly with careful monitoring for adverse reactions, and the infusion should be immediately discontinued if any reactions occur. Side effects can be classified as:

- Local – injection site pain, skin pigmentation, metallic taste;
- Immediate systemic – urticaria, headache, fever, nausea, hypotension, anaphylactic shock, death;
- Late systemic – myalgia, arthralgia, lymphadenopathy [1, 9, 18,].

Iron preparations should be administered in an inpatient or outpatient setting where trained medical personnel are available to provide medical assistance in case of anaphylactic reactions. After each administration, the patient should be monitored for at least 30 minutes.

The criteria for treatment efficacy are as follows:

- Presence of a reticulocytic crisis on days 7-10 of therapy with iron preparations. Reticulocytosis is more pronounced in patients with a high degree of anemia and may be absent in those with a low degree of anemia;
- Disappearance of "pica chlorotica" signs of sideropenic syndrome within 2-3 weeks;
- Increase in hemoglobin (Hb) levels by the third week;
- Appearance of normochromic, normocytic erythrocytes alongside the hypochromic erythrocytes that were formed before the iron therapy.

Prevention of iron-deficiency anemia is recommended for pregnant and lactating women, growing children, adolescents, patients with a history of gastrectomy or gastro-jejunal anastomosis, patients with persistent causes of iron-deficiency anemia, and chronic blood donors [3, 8, 16].

Prognosis. The evolution and prognosis of iron-deficiency anemia are favorable, with a potential for cure (complete rehabilitation)

Follow-up. Patients will be under the supervision of their family doctor. General blood tests, along with serum iron and ferritin levels, should be performed every 6 months during the first 2-3 years [2, 13].

CLINICAL CASES

Patient P., a 36-year-old woman, complains of general weakness, dizziness, headache, and shortness of breath during physical exertion.

She has been unwell for the past year, during which these symptoms have appeared and gradually worsened. She reports a craving for eating raw pasta. Menstruation began at the age of 14, lasting 5-6 days with a heavy flow. Her obstetric history includes three childbirths and two miscarriages.

Objective data: The patient is in a satisfactory general condition. The skin is dry and pale. Fingernails are fragile with longitudinal striations and break easily. Peripheral lymph nodes are not palpable. Internal organs show no abnormalities.

General blood analysis: Hb-98 g/l, erythrocytes – $3,5 \cdot 10^{12}$/l, MCV – 73,2,2 fl, MCH-23,1 pg/cell, MCHC – 312 g/l, reticulocytes – 6‰, leucocytes – $5,2 \cdot 10^{9}$/l, platelets – $280,0 \cdot 10^{9}$/l (80‰), non-segmented 2%, segmented 68%, eosinophils 1%, lymphocytes 23%, monocytes 6%, ESR – 3 mm/hr, anisocytosis +, hypochromia ++.

1. Determine the provisional diagnosis.
2. Develop the investigation plan.
3. Establish the treatment plan.

Clinical case

Patient C., aged 28 years, presented to the doctor with complaints of general weakness, dizziness, headache, and shortness of breath during physical exertion. Further questioning revealed that the patient had a craving for eating chalk.

She has been experiencing symptoms for the past year.

She has no significant past medical history. The menstrual cycle lasts 5-6 days, with a heavy flow, sometimes accompanied by clots. She has had three pregnancies and two childbirths.

Objective: The patient has pale, dry skin. There is no evidence of hemorrhagic syndrome. The nails are thin, brittle and break easily. Peripheral lymph nodes are not palpable. A vesicular murmur is present in the lungs. Heart sounds are muffled but rhythmic. The pulse is of

satisfactory quality, with a rate of 82 beats per minute. Blood pressure is 120/70 mm/Hg. The abdomen is soft and non-tender on palpation. The spleen and liver are not palpable.

Blood analysis: Hb – 80 g/l, erythrocytes – $2,8 \cdot 10^{12}$/l, MCV – 62,1 fl, MCH – 19,2 pg/cell, MCHC – 309 g/l, reticulocytes – 8‰, leucocytes – $4,0 \cdot 10^{9}$/l, platelets – $280,0 \cdot 10^{9}$/l, non-segmented 4%, segmented 68%, lymphocytes 25%, monocytes 3%, ESR – 11 mm/hr. Hypochromia +++, anisocytosis +, poikilocytosis +.

1. Establish the diagnosis.
2. Determine the investigation plan.
3. Develop the treatment approach.

Clinical case

Patient I., 24 years old, presented to the doctor with complaints of general weakness, dizziness, and difficulty swallowing.

She reports experiencing these symptoms for the past 4-5 years.

She is the fourth child in her family**.** Her diet mainly consists of dairy products, and she enjoys eating cornmeal.

Her menstrual cycle began at the age of 13, lasting 4-5 days with a heavy flow, occurring every 28 days. She gave birth to her first child three years ago and breastfed until the child was one year old. One year ago, she gave birth to her second child.

Objective: The patient is in satisfactory condition. The skin is pale, clean, and dry.

The sclerae have a bluish tinge. The fingernails are brittle, thin, and stratified. Peripheral lymph nodes, spleen, and liver not palpable.

Blood analysis: Hb – 70 g/l, erythrocytes – $3,2 \cdot 10^{12}$/l, MCV – 61,4 fl, MCH – 18,4 pg/cell, MCHC – 307 g/l, reticulocytes – 2‰, leucocytes – $5,6 \cdot 10^{9}$/l, non-segmented 2%, segmented 64%, eosinophils 2%, lymphocytes 25% monocytes 7%, ESR - 15 mm/h, hypochromia ++.

1. Establish the provisional diagnosis and provide justification.
2. Draw up the patient's investigation plan (laboratory investigations, diagnostic instruments required and their sequence).
3. Indicate the treatment plan.

TESTS

S Iron treatment in iron-deficiency anemia is given:

A. Until Hb and erythrocyte indices normalize
B. For 2 months
C. For life
D. Until the gastrointestinal syndrome disappears
E. Until iron stores in the body are restored

S The most common cause of iron-deficiency anemia is:

A. Insufficient iron intake from the diet
B. Increased iron requirements of the body
C. Increased iron loss
D. Dysregulation of iron absorption
E. Diffuse atrophy of the stomach lining

S The underlying cause of sideropenic syndrome is:

A. Low hemoglobin
B. Deficiency of iron stores in the body
C. Tissue hypoxia
D. Diffuse atrophy of the gastric mucosa
E. Hyperthrombocytosis

S The clinical picture of iron-deficiency anemia includes the following:

A. Neurologic syndrome
B. Sideropenic syndrome
C. Proliferative syndrome
D. DIC syndrome
E. Hemorrhagic syndrome

S In patients with grade III iron-deficiency anemia, treatment begins with:

A. Parenteral iron therapy
B. Oral iron therapy
C. Parenteral and oral iron therapy
D. Red blood cell concentrate transfusions
E. Diet

S For iron-deficiency anemia, the following is correct:

A. It occurs in 8-15% of women of reproductive age
B. It occurs more often in men
C. It occurs in both women and men with equal incidence
D. It is the rarest form of anemia
E. It occurs less often than B_{12}-deficiency anemia

S For normal hematopoiesis, the following are needed daily:

A. 20-25 mg of iron
B. 5 g of iron
C. 1 g iron
D. 1 mg of iron
E. 100 mg of iron

S The evident clinical efficacy of iron therapy in patients with iron-deficiency anemia is observed:

A. Within 10 days
B. Within 7 days
C. Within 3 weeks
D. Within 2 months
E. Within 6 months

S The disappearance of the signs of „pica chlorotica" signs from sideropenic syndrome due to iron treatment is observed:

A. Within 10 days
B. Within 7 days
C. Within 2 months
D. Within 6 months
E. Within 2-3 weeks

S The most common cause of iron-deficiency anemia in men and menopausal women is:

A. Bleeding in the gastrointestinal tract
B. Dysregulation of iron absorption
C. Insufficient iron intake

D. Increased iron requirement
E. Transferrin deficiency

S The primary syndrome of iron-deficiency anemia is:
A. Splenomegaly
B. Neurologic
C. Sideropenic
D. Proliferative
E. Hemorrhagic

S Iron absorption occurs in:
A. The duodenum and proximal portion of the small intestine
B. The distal portion of the small intestine
C. The stomach
D. Throughout the small intestine
E. The terminal ileum

M The differential diagnosis of iron-deficiency anemia is most commonly made between:
A. B_{12}-deficiency anemia
B. Folic acid deficiency anemia
C. Aplastic anemia
D. Paroxysmal nocturnal hemoglobinuria
E. Thalassemia

M For iron-deficiency anemia, the following characteristics are correct:
A. Hemorrhagic syndrome
B. „Pica chlorotica”
C. Numbness in fingers and toes
D. Waxy skin
E. Angular stomatitis

M The characteristic manifestations of sideropenic syndrome are:
A. Brittle hair and nails
B. Jaundiced skin
C. „Pica chlorotica”

D. Splenomegaly
E. Lymphadenopathy

M Iron-deficiency anemia is manifested by:
A. Anemic syndrome
B. Hemorrhagic syndrome
C. Neurologic syndrome
D. Sideropenic syndrome
E. Proliferative syndrome

M The preparations used in the treatment of iron-deficiency anemia include:
A. Vitamin B_{12}
B. Folic acid
C. Polyvitamins
D. Folifer
E. Ferosom

M The development of iron-deficiency anemia may be caused by:
A. Hiatal hernia
B. Intrinsic factor deficiency
C. Gastrointestinal bleeding
D. Hemolytic crisis
E. Nonsteroidal anti-inflammatory drugs

M The causes of iron-deficiency anemia can be:
A. Insufficient iron intake
B. Increased iron requirement of the body
C. Diffuse atrophy of the stomach lining
D. Transcobalamin II deficiency
E. Deficiency of Castle factor

M A peripheral blood smear shows hypochromic erythrocytes, microcytosis. Which of the following can be associated with this hematologic appearance:
A. Angular stomatitis
B. Paresthesia in fingers and toes

C. Pronounced splenomegaly
D. Hemorrhagic syndrome
E. Sideropenic dysphagia

M Transfusion of erythrocyte concentrate in iron-deficiency anemia is justified in cases of:
A. Anemic precoma
B. Presence of sideropenic syndrome
C. Hb levels of 90-100 gr/l
D. Patients who have undergone total gastrectomy
E. Patients scheduled for surgery based on vital indications

M What morphological changes can be found in iron-deficiency anemia:
A. Hypersegmentation of neutrophil nuclei
B. Hypochromia of erythrocytes
C. Microcytosis
D. Ring erythrocytes
E. Target cells

M The manifestations characteristic of sideropenia syndrome are:
A. „Pica chlorotica”
B. Angular stomatitis
C. Neurological syndrome
D. Hemorrhagic syndrome
E. Sideropenic dysphagia

M In iron-deficiency anemia the following may be present:
A. Low serum iron levels
B. Decreased ferritin
C. Pallor and jaundice
D. Sideropenic dysphagia
E. Neurological syndrome

M For iron-deficiency anemia are characteristic:
A. Normoblastic hemopoiesis
B. Sideropenic syndrome

C. Erythrocyte hypochromia
D. Lack of sideropenic syndrome
E. „Pica chlorotica”

M The criteria for the effectiveness of treatment with iron preparations iniron-deficiency anemia are:
A. Reticulocytosis on the 7-10th day
B. Reticulocytosis on the 4th-5th day
C. Increased hemoglobin content starting from the third week
D. Disappearance of „pica chlorotica” signs from sideropenic syndrome in 2-3 weeks
E. Appearance of erythrocytes saturated with hemoglobin

M Dysregulation of iron absorption occurs in cases of:
A. Billroth I stomach resection
B. Billroth II stomach resection
C. Chronic enteritis
D. Malabsorption syndrome
E. Extensive resection of the small intestine in the proximal part

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